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Table 1. Level 1 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 5%
Disintegrant	
starch	+/- 3%
other	+/- 1%
Binder	+/- 0.5%
Lubricant	
calcium or magnesium stearate	+/- 0.25%
other	+/- 1%
Glidant	
talc	+/- 1%
other	+/- 0.1%
Film coat	+/- 1%

Table 2. Level 2 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 10%
Disintegrant	
starch	+/- 6%
other	+/- 2%
Binder	+/- 1%
Lubricant	
calcium or magnesium stearate	+/- 0.5%
other	+/- 2%
Glidant	
talc	+/- 2%
other	+/- 0.2%
Film coat	+/- 2%

(57) Abstract: A method is disclosed to verify and identify pharmaceutical products through their product signatures in order to
combat counterfeiting and reduce dispensing errors, using methods such as near infrared spectroscopy. Furthermore, in order to actively
evade pharmaceutical product counterfeiting, a method is disclosed where an amount of one or more of the inactive ingredients is
varied over time; the variation provides a different product signature, but falling within a level deemed permissible by a regulatory
body.

FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Drug Authentication

BACKGROUND

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Field of the Invention

This invention relates generally to a method for assuring drug and drug product identity as a product is distributed from the manufacturer to the retailer and to the patient. This invention

10   allows for the active evasion of the counterfeiting of pharmaceutical products.

Within the distribution system of drugs and drug products, there is a need to assure drug and drug product identity. Example scenarios include the need to identify and differentiate authentic and counterfeit drug products, and a need to assure the dispensing of the correct

15   drug product to patients from pharmacies. There also exists the need to authenticate the manufacturer of drugs after they leave the pharmacy, such as when a drug is allegedly involved in causing injury to a patient.

Drug product counterfeiting is a significant and growing world-wide problem. There are

20   about 9 billion subscriptions filled worldwide each year; about 3 billion prescriptions are filled in USA. It has been estimated that about 10 to 50 percent of prescription drugs in certain countries of Asia, Africa, and South America may be counterfeit. The number of counterfeit drug cases being investigated by the FDA has quadrupled and includes such well known drugs as Lipitor, Procrit, Neupogen, Serostim, Zyprexa, Viagra, and Evra. Drugs are now

25   purchased in increasing quantities over the Internet and from Canadian and Mexican pharmacies making source and drug identification even harder.

In "Combating Counterfeit Drugs: A Report of the Food and Drug Administration", a number of different technologies to prevent counterfeiting are discussed, such as multi-pronged

30   approaches utilizing tag technologies (e.g. truck-and-trace) pedigree papers, an electronic package code (EPC), bar codes, radio frequency ID (FRID), special inks, holograms, strengthening state licensure requirements for wholesale distributors, and continuing development and implementation of secure business practices. Also discussed is requiring

manufacturers to sell products only to wholesalers who only directly purchase from the
manufacturer and requiring manufacturers to publish the names of their wholesalers on their
Web sites

In addition to problems of counterfeiting, with the increasing number of prescriptions being
5   filled, there is an increased chance for prescription error. While these errors may take many
forms, the likelihood of a dangerous or life threatening "adverse drug event" increases
proportionally with the increased chance of prescription fill error. Several studies have shown
that prescription error rates are consistently in the 2% to 7% range, with a 4% error rate often
cited as a reliable average.

10   Many systems have been devised to apply identifying markers to drugs, such as color, size
and shape distinctions among different drugs or on the same drug from different
manufacturers. Identification markers applied to drugs are typically discernible to a
prospective counterfeiter and can therefore be reproduced by the counterfeiter in many cases.

15   One of the problems confronting marking systems relating to drugs is the need to provide
unadulterated drugs, i.e. drugs which the FDA considers to be subject to federal guidelines
and which meet those guidelines. Thus, the addition of marker substances to a dosage form,
although not discernable without sophisticated analysis procedures, must meet regulatory
approval and is typically subject to onerous reporting requirements. Furthermore,
20   counterfeiters can also analyze the drug for the presence of the marker and thereafter
duplicate the marker containing drug.

Thus, there exists an unfulfilled need for a drug identification system which is covert, which
is within governmental guidelines for pharmaceutical quality, which can quickly determine
25   the source and/or identity of the drug as to manufacturer, including the production lot, and
which, optionally, may be maintained in confidence from the identification system user.
Ideally, the identification system is a dynamic system that changes over time, thereby
rendering efforts to break the system even more unlikely to be successful.

30   <u>Description of Related Art</u>

Color, shape size and external markings have long been used to identify drugs in solid dosage
forms to be used in conjunction with external container labeling schemes.

There are examples of overt drug labeling systems known to the art. Baum, USP 4,918,604, describes a drug labeling and prescription filing system. The system identifies the dispensed drug to be identified via a color photograph of the drug on its packaging.

5   An example using a combination of overt methods is disclosed in Wootton, USP 6,535,637 and entitled Pharmaceutical Pill Recognition and Verification System. The system utilizes a combination of coloration, shape, size and other surface features of the pill or tablet.

A scheme using covert identification of a drug by spectral means is disclosed in Soloman, 10   USP 5,679,954 entitled Non-Destructive Identification of Tablet Dissolution by Means of Infared Spectroscopy and USP 5,900,634 entitled Real-Time On-Line Analysis of Organic and Non-Organic Compounds for Food, Fertilizers, and Pharmaceutical Products. Soloman provides an apparatus for infrared spectroscopy using a succession of collimated light beams throughout the middle and near infrared spectrum. These beams are impinged against the 15   sample and the diffuse component of the reflected light is measured throughout the spectrum. Finally, the light received is analyzed by a neutral network to determine the sample characteristics.

Rzasa et al., USP 6,771,369, entitled System and Method for Pharmacy Validation and Inspection, discloses an apparatus for verifying the identity of a dispensed pharmaceutical. 20   An analysis unit adapted to determine a property of the dispensed pharmaceutical, an input device adapted to receive predetermined identifying information corresponding to the dispensed pharmaceutical, and a comparison unit adapted to compare the determined property of the dispensed pharmaceutical with the predetermined identifying information. Rzasa et al. also discloses a method of verifying a prescription, wherein the prescription comprises a 25   pharmaceutical compound, by associating the prescription with a unique identifier, storing the unique identifier, determining the identity of the pharmaceutical compound, and comparing the identity of the pharmaceutical compound with the unique identifier.

BRIEF SUMMARY OF THE INVENTION

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This present disclosure uses spectral analyses, such as near-infrared (NIR) spectroscopy, to verify and identify pharmaceutical products through their product signatures. . A method is

disclosed where an amount of one or more of the inactive ingredients in the pharmaceutical product is varied over time; the variation providing a different product signature, but falling within a level deemed permissible by a regulatory body. This method results in the convert inclusion of unique product signatures that can be changed over time

5   between batches of product, resulting in an authentication system that is difficult to deceive by potential counterfeiters.

The marking system is covert since the authentication system employs a pharmaceutical product's NIR spectrum. The marking system is inherent in the drug itself, is present in each

10   solid dosage form of the drug, and cannot be modified after manufacture. Inert ingredients in the dosage form are changed over time, the spectral signature of the dosage form is determined by the producer [reference] or third party vendor setup for such purposes and an unknown sample has its spectral signature compared to the spectral signature of the reference. The match or lack of match of the two spectral signatures determines whether or not the

15   dosage form was produced by that manufacturer, and, if produced by that manufacturer, which batch, lot, plant, manufacturing line, or time of manufacture, etc. the set of dosage forms the sample belongs to.

The present method allows a manufacturer to "fingerprint" or "authenticate" a selected

20   quantity of manufactured drug, be it by batch, by production location, by production line, by date of manufacture, etc. The word "authenticate" as used herein refers to analysis based on a parameter or set of parameters associated with a pharmaceutical product that allows an observer to determine some fact relating to the product and thereafter to compare that fact to a reference standard. Information developed may be used to identify the drug, such as a

25   therapeutic agent, a non-therapeutic agent (excipient), an origin, dosage level, and the like.

Due to its flexibility in determining the number of dosage forms manufactured with a single product signature, the manufacturer can use the methods of the present invention for quality assurance, quality control, or other internal or external control purposes. The product

30   signature is used in conjunction with packaging information to confirm lots, batches or any other identifying information as the pharmaceutical product moves through the supply chain.

These benefits are obtained by verifying and/or determining identity of pharmaceutical products within a drug product distribution system, and are achieved though the use of NIR

techniques optionally in connection with one or more other technologies. The combination of these techniques and approaches make for a rapid and accurate approach to assure drug and drug product identity, as well as a method to prevent the pharmaceutical product from being counterfeited.

5

The methods also provide an efficient technique for fingerprinting drugs as to the manufacturer and production batch. Most significantly, the techniques disclosed provide for systems and methods of manufacturing a unique fingerprint that serves as a label or product signature inherent in each pharmaceutical product or batch thereof. Advantageously, the

10 reference product signature is selectively disclosed and easily coordinated through the manufacturer of the pharmaceutical product.

The herein disclosed approach is to apply NIR spectroscopy with a manufacturing method that provides for a dynamic tag system. Future tags are not anticipatable and perhaps not

15 practically detectable since formulation component(s) themselves provide the tag.

In certain embodiments, the manufacturing method complies with regulatory mechanisms that were implemented in 1995 (immediate release products) and 1997 (modified release products) to minimize regulatory review or reporting requirements. The method may be

20 modified as regulatory or equipment changes occur to maintain or increase the number of signatures that may be used.

NIR spectrometry is advantageous in terms of time and disposables. NIR is noninvasive and nondestructive. Analysis times are very short (e.g. 1 sec) and additional reagents are not

25 required. The procedure is highly sensitive and is able to can perform multi-component analyses, as disclosed herein. Moreover, the disclosed procedures require little, if any, sample preparation.

In one of its various embodiments, the present invention is a method of labeling a

30 pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising varying an amount of at least one of the one or more inactive ingredients over time and generating a product signature of the pharmaceutical product having the varied amount of the at least one of the one or more inactive ingredients.

The present invention includes a batch identification method for determining the source
of a pharmaceutical product from among a plurality of production batches of the
pharmaceutical produt, where the pharmaceutical product has one or more active ingredients
and one or more inactive ingredients, comprising changing an amount of at least one of the
one or more inactive ingredients among different batches of the pharmaceutical product
produced, the variation being at least sufficient to distinguish the difference in the NIR
spectra of product produced in each batch.

Also disclosed is a system for verifying the authenticity of a pharmaceutical product
comprising the steps of: manufacturing more than one batch of a pharmaceutical product,
each batch having a reference spectral signature; inputting each of the reference spectral
signatures into a database; scanning a sample pharmaceutical product to produce a scanned
spectral signature; comparing the scanned spectral signature to each of the reference spectral
signatures; and reporting the results of the comparison, wherein the authenticity of the sample
pharmaceutical product is verified by the scanned spectral signature being equivalent to at
least one of the reference spectral signatures.

In another of its embodiments the invention comprises a set of groups of a pharmaceutical
product having one or more active ingredients and one or more inactive ingredients, wherein
the one or more active ingredients and the one or more inactive ingredients are the same in
each group in the set, and an amount of at least one of the one or more inactive ingredients is
different in at least one group of the set as compared to the other groups in the set, wherein
the amount is detectable in a near-infrared (NIR) spectra of the pharmaceutical product in the
at least one group of the set as compared to a near-infrared (NIR) spectra of the
pharmaceutical product of the other groups of the set.

As used in this disclosure, a "set" of groups of pharmaceutical products means a plurality of
groups where each group is related to the other groups in the set by having the same active
and inactive ingredients present in the pharmaceutical product, each group being
distinguished from other groups in the set by having varying amounts of one or more of the
inactive ingredients in the pharmaceutical product.

The invention also includes member[s] of a set of groups of a pharmaceutical product having
one or more active ingredients and one or more inactive ingredients, wherein the one or more

active ingredients and the one or more inactive ingredients are the same in each group in the set, and an amount of at least one of the one or more inactive ingredients is different in at least one group of the set as compared to the other groups in the set, wherein the amount is detectable in a near-infrared (NIR) spectra of the pharmaceutical product in the at least one group of the set as compared to a near-infrared (NIR) spectra of the pharmaceutical product of the other groups of the set.

In yet another embodiment, the present invention is a method of manufacturing a labeled pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising modifying the quantity of at least one of the one ore more inactive ingredients in a first pharmaceutical product to make a second pharmaceutical product, wherein the modification is detectable in an near-infrared (NIR) spectra of the second pharmaceutical product as compared t a near-infrared (NIR) spectra of the first pharmaceutical product, wherein said second pharmaceutical product is the labeled pharmaceutical product.

The present invention further includes a labeling system for a pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising modifying a quantity of at least one of the one or more inactive ingredients in a first pharmaceutical product to make a second pharmaceutical product, wherein the modification is detectable in a near-infrared (NIR) spectra of the second pharmaceutical product as compared to a NIR spectra of the first pharmaceutical product, wherein said second pharmaceutical product comprises the label.

In yet another of its various embodiments, the present invention discloses a method of determining the identify of a pharmaceutical product comprising the steps of obtaining a product signature of said pharmaceutical product and comparing said product signature to a reference product signature of a reference pharmaceutical product, wherein said reference product signature is a member of a library, wherein the pharmaceutical product is identified as the reference pharmaceutical product if the product signature of the pharmaceutical product is the same as the reference product signature.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 contains Table 1. Level 1 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms and Table 2. Level 2 Component and Composition
5 Changes for Immediate Release Oral Solid Dosage Forms

Figure 2 contains Table 3. Level 3 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms and Table 4. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)
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Figure 3 contains Table 5. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient) and Table 6. Level 3 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)
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Figure 4 contains Table 7. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient); Table 8. Level 2 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (release controlling excipient); and Table 9. Level 3 Component and Composition Changes
20 for Modified Release Oral Solid Dosage Forms (release controlling excipient)

Figure 5 contains Table 10. Schematic of areas of use within the commercial pipeline

Figure 6 contains Table 11. Composition of Aspirin Formulations; Table 12. Composition of
25 Prednisone Formulations; Table 13. Composition of Indomethacin Formulations; and Table 14 Compositions of Acyclovir Formulations.

Figure 7 contains Table 15. This is a chart of the 2nd Derivative of Absorbance Versus Wavelength: Aspirin Formulations where formulations A3 (Yellow), A1 (Blue), and A2
30 (Red) contained increasing amounts of microcrystalline cellulose, the intensities around 1995 nm and 2055 nm reflect NIR to differentiate the formulations and the profiles of pure microcrystalline cellulose (Light Blue) and pure aspirin (Green) are also shown.

Figure 8 contains Table 16. This is a chart of the 2nd Derivative of Absorbance Versus
Wavelength: Prednisone Formulations where formulations B3 (Yellow), B1 (Blue), and B2
(Red) contained increasing amounts of magnesium stearate, the intensities around 1705 nm,
as well as the regions between 1725-1735 nm and 1775-1790 nm, reflect NIR to differentiate
the formulations and the profile of pure magnesium stearate (Light Blue) is also shown.

Figure 9 contains Table 17. This is a chart of the 2nd Derivative of Absorbance Versus
Wavelength: Indomethacin Formulations where formulations C3 (Yellow), C1 (Blue), and C2
(Red) contained increasing amounts of microcrystalline cellulose, as well as decreasing
amounts of croscarmellose sodium, the intensities around 1890 nm and 1920 nm reflect NIR
to differentiate the formulations and the profiles of pure microcrystalline cellulose (Light
Blue) and pure croscarmellose sodium (Purple) are also shown.

Figure 10 contains Table 18. This is a chart of the 2nd Derivative of Absorbance Versus
Wavelength: Acyclovir Formulations where formulations C3 (Yellow), C1 (Blue), and C2
(Red) contained increasing amounts of microcrystalline cellulose, as well as decreasing
amounts of starch where the intensities around 2175 nm, 2205 nm, 2225 nm, 2250 nm, 2265
nm, 2320 nm, 2345 nm, 2365 nm, as well as the regions between 2100-2130 nm and 2380-
2420 nm, reflect NIR to differentiate the formulations, and the profiles of pure
microcrystalline cellulose (Gray) and pure starch (Light Blue) are also shown.

DETAILED DESCRIPTION OF THE INVENTION

When used in this specification, the following words and phrases have the following
meanings ascribed to them.

A "pharmaceutical product" is a dosage form that comprises one or more therapeutic agents
and one or more inactive ingredients.

"Therapeutic agents" include natural [biologics] drugs, synthetic drugs and nutraceuticals.

"Dosage forms" include, by way of example, tablets, capsules, powders, solutions,
semisolids, suppositories, and lyophilized and milled powders, which may be reconstituted
for injection.

"Drugs" include by way of example, atorvastatin calcium, azithromycin, amlodipine besylate, carbamazepine, ceftriaxone sodium, clozapine, epoetin alfa, filgrastim, indinavir sulfate, isotretinoin, lamivudine/zidovudine, leuprolide acetate, olanzapine, phenytoin sodium, somatropin, trovafloxacin mesylate, and warfarin sodium.

"Nutraceuticals" include by way of example, feverfew, ginkgo biloba, saw palmetto, St. John's Wort, chondroitin sulfate, Coenzyme Q10, glucosamine, growth hormones, L-carnitine, L-phenylalanine, shark cartilage, vegetable concentrates, chromium picolinate, manganese, biotin, riboflavin, and ascorbic acid.

The identity of a pharmaceutical product minimally denotes the therapeutic agent (or therapeutic agents) contained in the pharmaceutical product, the dose or concentration of each therapeutic agent in the pharmaceutical product, and manufacturer of the pharmaceutical product or any combination thereof.

"Counterfeit" denotes a product that has been mislabeled or otherwise adulterated with respect to identity and/or source. A product manufactured by an unapproved source is counterfeit.

A "counterfeit pharmaceutical product" is dosage form that is counterfeit and which may or may not comprise a therapeutic agent.

Authentic denotes not being counterfeit. An authentic pharmaceutical product is a pharmaceutical product that is not counterfeit.

A" dispensing error" is the dispensing of a pharmaceutical product which is not the pharmaceutical product specified in the dispensed prescription label.

A "product signature" is the spectral features obtained from a pharmaceutical product or counterfeit pharmaceutical product that is subjected to one or more spectral analyses. Methods of spectral analysis include near-infrared (NIR) spectroscopy, Raman spectroscopy, and laser induced fluorescence (LIF) spectroscopy. An example of a product signature is the near-infrared spectrum of a specific lot of prednisone tablets that were produced by a

specific manufacturer. Near-infrared spectrum is the absorption spectrum between 400 and 2500 nm.

A" library" of product signatures is a collection of product signatures.

An" inactive ingredient" is a component of a pharmaceutical product which has no intended therapeutic effect; inactive ingredients are also known as excipients.

In the method disclosed, covert NIR spectral fingerprints are embedded into each lot of a pharmaceutical formulation by modifying formulation ingredient quantities while remaining within regulatory agency allowed composition changes. Among the significant benefits of this approach are no need for an external taggant and minimal regulatory burden. By intentionally varying excipient quantities within allowed ranges, it is possible to encode a unique fingerprint into each product lot.

Counterfeit drug products are an increasing problem, particularly because counterfeiting technology and counterfeitors have become more savvy. There remains a need to detect counterfeit drugs, including counterfeit drugs that are prepared and/or packaged similarly to the authentic pharmaceutical products. The invention includes but is not limited to the use of near-infrared (NIR), Raman and LIF (laser induced fluorescence) spectroscopy (all possible methods will hence be referred to as spectral methods or NIR methods) to identify the source of a drug in particulate dosage form and/or packaging. Advantages of NIR spectroscopy include its non-invasiveness, potential for low detection limits, rapidity of analysis (approximately 1 second), and minimal or no sample preparation. The vast majority of components commonly found in a pharmaceutical product exhibit a NIR spectrum.

Either or both the pharmaceutical packaging or dosage form can serve as taggants. For example, embossing, imprinting, printing, coating, dosage form size, and other identification methods can be applied to change the physical appearance of the dosage form (e.g. subtle changes in logo, use of an ultraviolet-dependent dye). Such approach can be used alone or in combination with other modifications of packaging and/or changes in the dosage form.

In a particular embodiment, the components in the dosage form can be varied, approximately batch-to-batch or with other [arbitrary] frequency, to provide a distinctive spectral signature for the product from that batch or lot.

5   Components of an oral particulate dosage forms (e.g. tablets or capsules) include the drug (active ingredient), impurities, drug degradents, fillers, disintegrants, binders, lubricants, glidants, colorants, flavoring agents, and coating materials. Some or all of the component levels can be modified, either batch-to-batch or with some other frequency, to yield a NIR spectra for the batch, a set of batches or other identification of lots.

10

Utilizing the procedures disclosed herein, the NIR spectra would not be identical for all product lots. A certain batch of product, or certain set of product batches, will have a unique composition, and hence a unique NIR spectra. The NIR spectrum of a particular lot is disclosed solely to those persons or entities selected by the manufacturer. Only the

15   manufacturer (or agents of the manufacturer) will know the composition and associated NIR spectra of products from a particular batch or lot.

A suspect product can be subjected to NIR analysis and cross-referenced against the authentic NIR spectra. The association between authentic product's batch number and its NIR spectra,

20   along with the ease of measuring NIR spectra, provides a basis to combat counterfeit drugs, to allow quality control and to identify lots for sundry other purposes.

Of added benefit, the association between NIR spectra and batch number(s) need not be provided to regulatory agencies or enforcement officials or health care providers, who could

25   still perform field sampling and relay NIR spectra to the manufacturer. The manufacturer would then report back only the information of whether or not the sample matches the lot associated with that spectrum.

Furthermore, because the manufacturer would arbitrarily vary the variation of ingredients

30   within the drug, past compositions (i.e. past NIR spectra of previous batches) would not be indicative of future compositions (i.e. future NIR spectra). Hence, a counterfeit effort would have no target product to counterfeit, without detection.

This approach employs the visible and NIR region of the electromagnetic spectrum. The NIR region typically includes wavelengths between about 700 nm (near the red in the visible spectrum) and about 3000 nm (near the infrared stretches of organic compounds). NIR absorbance peaks originate from overtones and combinations of the fundamental (mid-IR)

5   bands and from electronic transitions in the atoms. C-H, N-H, and O-H bonds are responsible for most of the major absorbances. NIR spectrometry is used chiefly to identify or quantify molecules, including unique hydrogen atoms. NIR spectrometry is used to analyze for water, alcohols, amines, and any compounds containing C-H, N-H, and/or O-H groups. Many other bond combinations also provide NIR absorbance peaks. The visible region includes

10 wavelengths between about 400 nm to about 700 nm. Absorbance peaks in this region can originate from conjugated pi electrons or aromatic moieties. Lakes and dies commonly used to give a dosage from a unique color typically absorb in this region of the electromagnetic spectrum

15 While a pharmaceutical product typically has only one formula, and while manufacturers typically avoid manufacturing changes, this new approach to combat counterfeiting relies on the availability of several (i.e. more than one) formulas for the marketed product.

The U.S. Food and Drug Administration (FDA) allows for a range of component and

20 composition changes in the manufacturing of products, without onerous regulatory requirements. The Center for Drug Evaluation and Research [CDER] publishes a series of monographs in its "Guidance for Industry" series. Its monographs "Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation" [SUPAC monographs] deal with changes in

25 various dosage forms and allowable changes in those dosage forms and reporting requirements relating to those changes. Monograph CMC 5 entitled "Immediate Release Solid Oral Dosage Forms" provides for certain changes in excipients in immediate release dosage forms in section "III. Components and Composition". CMC 8 is the analogous document relating to modified release dosage forms.

30

Section III of these monographs relates to changes in excipients [but not active components] in drug products and categorizes changes in excipient levels into three groups. In the case of immediate release and modified release oral solid dosage forms, changes are denoted Level 1, Level 2, and Level 3 type changes. Level 1 changes are those that are unlikely to have any

detectable impact on formulation quality and performance; regulatory filing documentation of a Level 1 change is limited to the Annual Report. Level 2 changes are those that could have a significant impact of formulation quality and performance. Level 3 changes are those that are likely to have a significant impact of formulation quality and
5   performance. Tests and filing documentation for a Level 2 change and a Level 3 change each vary depending upon three factors: drug therapeutic range, drug solubility, and drug permeability. Tables 1-9 describe these manufacturing changes.

The present invention may be used within any countries public health infrastructure. In such
10   cases, the skilled artisan is aware of obtaining and applying the appropriate regulatory guidelines in the manners referred to in the non-limiting exemplary embodiments provided herein.
For example, in the United States, a Level 1 change requires less burdensome regulatory documentation, and represents one preferable example, relative to Levels 2 or 3 to vary
15   formulation. Level 1 documentation requires one batch on long-term stability reported in an annual report. No additional dissolution documentation or in vivo bioequivalence documentation is required.

Hence, Level 1 changes are a preferable approach to tag authentic product, in order to avoid
20   counterfeiting and facilitate the detection of counterfeiting through NIR spectroscopy. This approach avoids the use of a taggant that is fixed, or is one which is included in the formulation for the sole purpose as a taggant. Our approach to use the formulation's components themselves facilitates the tagging effort, and does so in a more subtle fashion, such that this tagging effort is less detectable and hence less counterfeitable.

25

For example, for each immediate and modified release oral solid dosage forms, a filler can be modified by as much as 5% to provide a NIR spectra that tags the authentic product, and still qualify as a Level 1 change. Given the ability of NIR spectroscopy to resolve 1% and smaller differences in formulation, a unique tag can be fabricated by varying the filler level.
30   Moreover, the number of unique NIR signatures can be generated in a multiplicative fashion by modulating two or more components (e.g. vary filler, disintegrant, and binder). Varying filler over 11 levels, disintegrant over 7 levels, and binder over 3 level can results in 231 unique NIR spectra, or more.

It should be noted that the number of distinct spectra that can be obtained and/or used is limited only be the sensitivity of the test equipment. As the ability of the apparatus to distinguish among varying spectral data sets becomes greater, the number of tags available will increase and the required degree of excipient change will diminish

A further limit on the system relates to the quality of the manufacturing process. As process controls become even more precise and the desirability of having such controls becomes known, manufacturing practices will be held to tighter tolerances and a greater number of different spectral signatures will become available.

It is contemplated that the spectral signature of different product groups will be used for quality assurance purposes and will be able to identify product produced by different manufacturers, different manufacturing facilities of the same manufacturer, different production lines within a manufacturing facility, or product produced by different shifts on the same line in a manufacturing facility.

By varying the signature over time, environmental effects on the product in the field can be tracked and maintained in a database. Varying signatures over time also allows inherent determination of product dating and whether the product in question is a post-expiration product.

While NIR spectroscopy has some previous limited application in pharmaceutical analysis, it has not been applied to combat counterfeit drugs. Our approach employs the formulation itself to provide a dynamic tag system and NIR spectroscopy. It does not employ a fixed tag or a tag whose sole function is to serve as a tag, and thus subject to counterfeiting.

The approach of applying NIR spectroscopy to a manufacturing method that provides for a dynamic tag system is novel. Future tags are not anticipatable, and perhaps not practically detectable since formulation component(s) themselves provide the tag. The manufacturing method makes use of regulatory mechanisms that were implemented in 1995 (immediate release products) and 1997 (modified release products), in order for the tag system to be dynamic, yet viable from a regulatory point of view.

NIR spectrometry is advantageous in terms of time and disposables. Analysis times are very short (e.g. 1 sec). It is sensitive to multi-component variables, as planned in the described approach. There is essentially no sample preparation. NIR is noninvasive and nondestructive. No reagents are required. Detection limits can be very low.

5

Also, because this device can detect the drug type and its dose this could also be used to greatly minimize the possibility of the pharmacist dispensing the wrong drug and the wrong dose of a drug

10   In one embodiment, a unique NIR signature is engineered into the packaging as well as the product, much like a certificate of authenticity on a CD or commercial software package. A company could have several hundred types and assign a lot number to each one.

It should also be noted that varying the formulation to evade and detect counterfeiting is one
15   approach in the application of spectral methods. Another approach does not make use of the intentional periodic variation of the formulation as described above.

Various applications for this technology include, but are not limited to methods to evade and detect counterfeit drug products (and counterfeit drug substances and counterfeit
20   excipients); methods to assure drug product distribution integrity (and drug substance integrity and excipient integrity) at different levels for monitoring drug product distribution, such as by pharmaceutical manufacturers, pharmaceutical wholesalers, pharmaceutical distributers, and pharmacies (who would be interested in detecting counterfeit drug products and in assuring the correct product is being dispensed.), pharmaceutical repackagers, and
25   FDA field monitoring, as well as regulators in other countries.

A typical example application is in the detection of counterfeit drug products by FDA field inspectors and/or health care workers (e.g. pharmacist, nurse) working with the manufacturer of the authentic product. FDA field inspectors and/or health care workers would obtain the
30   NIR spectrum of suspect products and relay the spectrum data to the manufacturer of the authentic product. Agents of the manufacturer of the authentic product could also inspect samples in the field by obtaining NIR spectrum of suspect products.

Another typical example of its use would be by pharmacies employing NIR to avoid
accidental overdose or misadventure in pharmacy dispensing by assuring that the dispensing
robot dispenses the correct product or to assure the dispensed product is the correct product
with semi-automated dispensing devices where the NIR is built into tablet/capsule counter.

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In one of its embodiments, the comparison data needed to reference the sample against
authentic product is supplied to the field [the pharmacy, hospital or other dispensing
authority] to allow them to determine the authenticity of the drug in the field.

10   In an alternative embodiment a more secure system is utilized, where the drug manufacturer
maintains a comprehensive database of all variations of the drug dosage form over time and
allows access to that database to authorized users to allow a multiplicity of data to be
retrieved about the particular product being tested.

15   In a yet more secure variation, the manufacturer's central database reports only a yes:no
answer as to whether the product is counterfeit or outdated, allowing the manufacturer to
track the movement of its product through the supply chain but still maintain control over the
dissemination of the information.

20   It is also contemplated that a central repository of such data may be set up by industry or
government to track and maintain the purity of medicaments used by its citizens.

The following example is presented in order to more fully illustrate the preferred
embodiments of the invention. It should in no way be construed, however, as limiting the
25   broad scope of the invention.

Example 1

Materials. The following drug substances and excipients were used as received: aspirin
30   (Spreetrum, Gardena; CA), prednisone (Sigma; St Louis, MO), indomethacin (Spectrum;
Gardina, CA), acyclovir (Spectrum; Gardena, CA), microcrystalline cellulose (Emocel 90M,
Mendell; Patterson, NY), magnesium stearate (Spectrum, Gardina, CA), croscarmellose
sodium (FMC Biopolymer; Princeton, NJ), starch (Lycatab C, Roquette; Lestrem, France),
and lactose monohydrate (Super-tab, The Lactose Company; Hawera, New Zealand),

Formulation Methods. Three tablet formulations were designed and evaluated for each of four drugs, such that 12 formulations were made. The four drugs were aspirin, prednisolone, indomethacin, and acyclovir, and are denoted as drug A, B, C, and D, respectively. The

5   drugs differ in their therapeutic uses, physicochemical properties, spectral properties, and dose ranges. For each drug, three tablet formulations were fabricated. Tables 1-4 describe the composition of the 12 formulations and refer to formulations A1, A2, A3, B1, etc. In each table, the first formulations is denoted the reference formulation (i.e. A1, B1, C1, and D1 are reference formulations). For each drug, the formulations were varied within the

10   SUPAC level 1 tolerances by varying one or more excipients, relative to the reference formulation, resulting in the second and third formulations (i.e. formulations A2 and A3 were variants for formulation A1; formulations B2 and B3 were variants for formulation B1).

Variant formulations were attained through the following changes, relative to the reference.

15   For aspirin, microcrystalline cellulose was increased and decreased. For prednisone, magnesium stearate was increased and decreased. For indomethacin, microcrystalline cellulose and croscarmellose sodium were simultaneously varied. For acyclovir, microcrystalline cellulose and lactose monohydrate were simultaneously varied. In some cases the tablet weight changed.

20

Near-IR Methods. The formulations were scanned and analyzed by Foss NIRSystems Rapid Content Analyzer™. The following test conditions were used. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was 400 nm to 2500

25   nm with samples collected every 2 nm. The raw spectral data were converted into absorbance and 2nd derivative values using Foss's Vision software package.

Since the active components or components in the drug dosage for are not varied in the disclosed system, it is apparent that the system is not constrained by the type of active

30   ingredient or combination of actives. It is within the ability and choice of a skilled artisan to chose the inactive ingredient or ingredients to vary in developing the various spectral profiles of a drug product regardless of its active ingredients.

It should also be apparent that the system is independent of the quantity of active ingredient in the dosage form and that the system may actually be used to provide a signature to distinguish among varying dosage forms.

5   While the system is not dependent upon the identity of the active ingredient or ingredients, it is recognized that the system may be most useful in conjunction with certain drugs that are more likely to be subject to theft, abuse or counterfeiting.

CLAIMS

1. A method of labeling a pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising varying an amount of at least one of the one or more inactive ingredients over time and generating a product signature of the pharmaceutical product having the varied amount of the at least one of the one or more inactive ingredients.

2. The method of claim 1 wherein the product signature comprises a near-infrared (NIR) spectra, and wherein the product signature comprises a label.

3. A batch identification method for determining the source of a pharmaceutical product from among a plurality of production batches of the pharmaceutical product, where the pharmaceutical product has one or more active ingredients and one or more inactive ingredients, comprising changing an amount of at least one of the one or more inactive ingredients among different batches of the pharmaceutical product produced, the variation being at least sufficient to distinguish the difference in the NIR spectra of product produced in each batch.

4. The method of claim 1, wherein the inactive ingredient whose amount is varied is selected from the group consisting of a filler, a disintegrant, a binder, a lubricant, a glidant, a film coat and combinations thereof.

5. The method of claim 4, wherein the inactive ingredient is the filler.

6. The method of claim 5, wherein the amount changed is in the range of about 5 percent based on a total weight of the product.

7. The method of claim 4 in which the inactive ingredient is the binder.

8. The method of claim 7, wherein the amount changed is in the rage of about 0.5 percent based on a total weight of the product.

9. The method of claim 4 in which the inactive ingredient is the disintegrant.

10. The method of claim 9, wherein the amount changed is in the range of about 3 percent based on a total weight of the product.

11. A system for verifying the authenticity of a pharmaceutical product comprising the steps of:

manufacturing more than one batch of a pharmaceutical product, each batch having a reference spectral signature;

inputting each of the reference spectral signatures into a database;

scanning a sample pharmaceutical product to produce a scanned spectral signature;

comparing the scanned spectral signature to each of the reference spectral signatures; and

reporting the results of the comparison, wherein the authenticity of the sample pharmaceutical product is verified by the scanned spectral signature being equivalent to at least one of the reference spectral signatures.

12. The system of claim 11 in which the reference spectral signature and the scanned spectral signature are NIR spectra.

13. The system of claim 11 in which the spectral signature of the scanned product is transmitted to a database of spectral signatures of authentic products, the scanned spectral signature is compared to the authentic spectral signatures in the database and reporting the results of the comparison are reported.

14. A set of groups of a pharmaceutical product having one or more active ingredients and one or more inactive ingredients, wherein the one or more active ingredients and the one or more inactive ingredients are the same in each group in the set, and an amount of at least one of the one or more inactive ingredients is different in at least one group of the set as compared to the other groups in the set, wherein the amount is detectable in a near-infrared (NIR) spectra of the pharmaceutical product in the at least one group of the set as compared to a near-infrared (NIR) spectra of the pharmaceutical product of the other groups of the set.

15. The method of claim 1, wherein the inactive ingredient whose amount is varied is selected from the group consisting of a filler, a disintegrant, a binder, a lubricant, a glidant, a film coat and combinations thereof.

16. The method of claim 15, wherein the inactive ingredient is the filler.

17. The method of claim 16, wherein the amount changed is in the range of about 5 percent based on a total weight of the product.

18. The method of claim 15 in which the inactive ingredient is the binder.

19. The method of claim 18, wherein the amount changed is in the rage of about 0.5 percent based on a total weight of the product.

20. The method of claim 15 in which the inactive ingredient is the disintegrant.

21. The method of claim 20, wherein the amount changed is in the range of about 3 percent based on a total weight of the product.

22. A member of a set of groups of a pharmaceutical product having one or more active ingredients and one or more inactive ingredients, wherein the one or more active ingredients and the one or more inactive ingredients are the same in each group in the set, and an amount of at least one of the one or more inactive ingredients is different in at least one group of the set as compared to the other groups in the set, wherein the amount is detectable in a near-infrared (NIR) spectra of the pharmaceutical product in the at least one group of the set as compared to a near-infrared (NIR) spectra of the pharmaceutical product of the other groups of the set.

23. The method of claim 1, wherein the inactive ingredient whose amount is varied is selected from the group consisting of a filler, a disintegrant, a binder, a lubricant, a glidant, a film coat and combinations thereof.

24. The method of claim 23, wherein the inactive ingredient is the filler.

25. The method of claim 24, wherein the amount changed is in the range of about 5 percent based on a total weight of the product.

26. The method of claim 23 in which the inactive ingredient is the binder.

27. The method of claim 26, wherein the amount changed is in the rage of about 0.5 percent based on a total weight of the product.

28. The method of claim 23 in which the inactive ingredient is the disintegrant.

29. The method of claim 28, wherein the amount changed is in the range of about 3 percent based on a total weight of the product.

30. A method of manufacturing a labeled pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising modifying the quantity of at least one of the one or more inactive ingredients in a first pharmaceutical product to make a second pharmaceutical product, wherein the modification is detectable in an near-infrared (NIR) spectra of the second pharmaceutical product as compared to a near-infrared (NIR) spectra of the first pharmaceutical product, wherein said second pharmaceutical product is the labeled pharmaceutical product.

31. A labeling system for a pharmaceutical product having one or more active ingredients and one or more inactive ingredients comprising modifying a quantity of at least one of the one or more inactive ingredients in a first pharmaceutical product to make a second pharmaceutical product, wherein the modification is detectable in a near-infrared (NIR) spectra of the second pharmaceutical product as compared to a NIR spectra of the first pharmaceutical product, wherein said second pharmaceutical product comprises the label.

32. A method of determining the identify of a pharmaceutical product comprising the steps of:
obtaining a product signature of said pharmaceutical product and

comparing said product signature to a reference product signature of a reference
pharmaceutical product, wherein said reference product signature is a member of a
library, wherein the pharmaceutical product is identified as the reference
pharmaceutical product if the product signature of the pharmaceutical product is the
5   same as the reference product signature.

Table 1. Level 1 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 5%
Disintegrant	
starch	+/- 3%
other	+/- 1%
Binder	+/- 0.5%
Lubricant	
calcium or magnesium stearate	+/- 0.25%
other	+/- 1%
Glidant	
talc	+/- 1%
other	+/- 0.1%
Film coat	+/- 1%

Table 2. Level 2 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 10%
Disintegrant	
starch	+/- 6%
other	+/- 2%
Binder	+/- 1%
Lubricant	
calcium or magnesium stearate	+/- 0.5%
other	+/- 2%
Glidant	
talc	+/- 2%
other	+/- 0.2%
Film coat	+/- 2%

Figure 1

Table 3. Level 3 Component and Composition Changes for Immediate Release Oral Solid Dosage Forms

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	Greater than +/- 10%
Disintegrant	
starch	Greater than +/- 6%
other	Greater than +/- 2%
Binder	Greater than +/- 1%
Lubricant	
calcium or magnesium stearate	Greater than +/- 0.5%
other	Greater than +/- 2%
Glidant	
talc	Greater than +/- 2%
other	Greater than +/- 0.2%
Film coat	Greater than +/- 2%

Table 4. Level 1 Component and Composition Changes for Modified Release Oral Solid Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 5%
Disintegrant	
starch	+/- 3%
other	+/- 1%
Binder	+/- 0.5%
Lubricant	
calcium or magnesium stearate	+/- 0.25%
other	+/- 1%
Glidant	
talc	+/- 1%
other	+/- 0.1%
Film coat	+/- 1%

Figure 2

Table 5. Level 2 Component and Composition Changes for Modified Release Oral Solid
Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	+/- 10%
Disintegrant starch other	+/- 6% +/- 2%
Binder	+/- 1%
Lubricant calcium or magnesium stearate other	+/- 0.5% +/- 2%
Glidant talc other	+/- 2% +/- 0.2%
Film coat	+/- 2%

Table 6. Level 3 Component and Composition Changes for Modified Release Oral Solid
Dosage Forms (nonrelease controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Target Dosage Form Weight
Filler	Greater than +/- 10%
Disintegrant starch other	Greater than +/- 6% Greater than +/- 2%
Binder	Greater than +/- 1%
Lubricant calcium or magnesium stearate other	Greater than +/- 0.5% Greater than +/- 2%
Glidant talc other	Greater than +/- 2% Greater than +/- 0.2%
Film coat	Greater than +/- 2%

Figure 3

Table 7. Level 1 Component and Composition Changes for Modified Release Oral Solid
Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	+/- 5%

Table 8. Level 2 Component and Composition Changes for Modified Release Oral Solid
Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	+/- 10%

Table 9. Level 3 Component and Composition Changes for Modified Release Oral Solid
Dosage Forms (release controlling excipient)

Excipient	Percent Excipient (w/w) Out of Total Release Controlling Excipient Content in the Modified Release Solid Oral Dosage Form
Any release controlling excipient(s)	Greater than +/- 10%

Figure 4

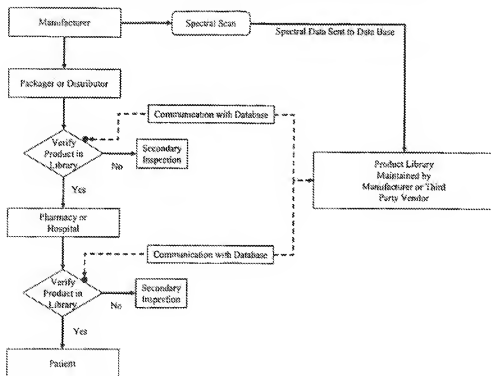Table 10. Schematic of use within the commercial pipeline

Figure 5

Table 11. Composition of Aspirin Formulations

Component	Formulation A1 (mg/tab)	Formulation A2 (mg/tab)	Formulation A3 (mg/tab)
Aspirin	325	325	325
Microcrystalline cellulose	73	83	63
Magnesium stearate	2	2	2
TOTAL WEIGHT	400	410	390

Table 12. Composition of Prednisone Formulations

Component	Formulation B1 (mg/tab)	Formulation B2 (mg/tab)	Formulation B3 (mg/tab)
Prednisone	5	5	5
Microcrystalline cellulose	94.5	94.5	94.5
Magnesium stearate	0.5	0.75	0.25
TOTAL WEIGHT	100	100.25	99.75

Table 13. Composition of Indomethacin Formulations

Component	Formulation C1 (mg/tab)	Formulation C2 (mg/tab)	Formulation C3 (mg/tab)
Indomethacin	25	25	25
Microcrystalline cellulose	71.5	74	69
Croscarmellose sodium	3	2	4
Magnesium stearate	0.5	0.5	0.5
TOTAL WEIGHT	100	101.5	98.5

Table 14. Compositions of Acyclovir Formulations

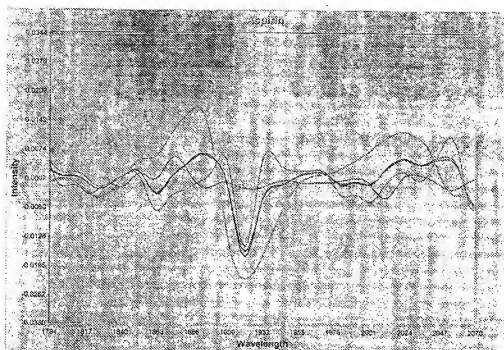| Component	Formulation D1 (mg/tab)	Formulation D2 (mg/tab)	Formulation D3 (mg/tab)
Acyclovir	200	200	200
Microcrystalline cellulose	113.26	120.26	106.26
Starch	35	27.99	41.99
Magnesium stearate	1.75	1.75	1.75
TOTAL WEIGHT	350	350	350

Figure 6

Table 15. 2nd Derivative of Absorbance vs. Wavelength: Aspirin Formulations

Figure 7

Table 16. 2nd Derivative of Absorbance vs. Wavelength: Prednisone
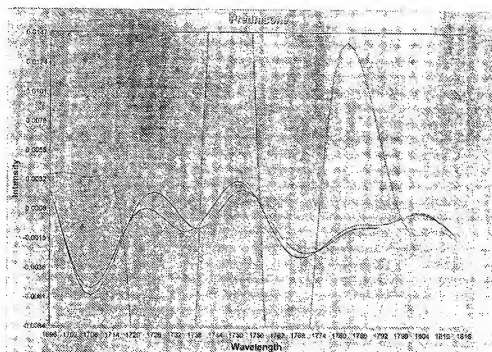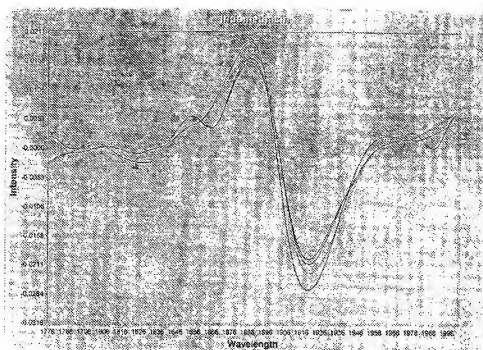Formulations

Figure 8

Table 16. 2nd Derivative of Absorbance vs. Wavelength: Prednisone
Formulations

Figure 8

Table 17. 2nd Derivative of Absorbance vs. Wavelength: Indomethacin
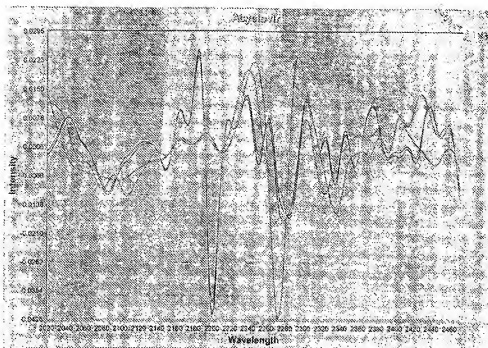Formulations

Figure 9

Table 18. 2nd Derivative of Absorbance vs. Wavelength: Acyclovir Formulations

Figure 10